Tracking single hematopoietic stem cells in vivo using high-throughput sequencing in conjunction with viral genetic barcoding.

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Public Summary:
A single cell may possess enormous power to rejuvenate or injure an organism as shown by many stem cell and cancer studies. However, it is technically challenging to track single cells in an organism. Here, we have developed a new technology that labels individual cells with unique DNA barcodes and simultaneously tracks them in the same organism using next-generation sequencing. To demonstrate this single cell tracking technology, we used it to track the development of individual hematopoietic (blood) stem cells in mice. We show how this technology is forty times cheaper and thousands of times more sensitive than conventional assays. We also show how this technology can provide new scientific information unattainable by previous assays. For example, our data provide the first evidence that individual hematopoietic stem cells do not equally contribute to blood production after irradiation and that they are regulated by at least two distinct modes in the same mouse. This single cell tracking technology can be applied to almost all mammalian cells and will help us to better understand cellular behavior at the single cell level.

Scientific Abstract:
Disentangling cellular heterogeneity is a challenge in many fields, particularly in the stem cell and cancer biology fields. Here we demonstrate how to combine viral genetic barcoding with high-throughput sequencing to track single cells in a heterogeneous population. We use this technique to track the in vivo differentiation of unitary hematopoietic stem cells (HSCs). The results are consistent with single-cell transplantation studies but require two orders of magnitude fewer mice. In addition to its high throughput, the high sensitivity of the technique allows for a direct examination of the clonality of sparse cell populations such as HSCs. We show how these capabilities offer a clonal perspective of the HSC differentiation process. In particular, our data suggest that HSCs do not equally contribute to blood cells after irradiation-mediated transplantation, and that two distinct HSC differentiation patterns co-exist in the same recipient mouse after irradiation. This technique can be applied to any virus-accessible cell type for both in vitro and in vivo processes.